

Ion Pair Extraction in Preparative Organic Chemistry

II. Preparation of Tetrabutylammonium Salts

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The nucleophilic displacement reaction is one of the most important reactions in preparative organic chemistry and has thus been extensively studied. The main problem associated with this reaction is that salts containing the appropriate anion are often not very soluble in organic solvents. This problem has been circumvented in several different ways neither of which is entirely satisfactory: 1. Reactions in an organic layer with the salt present as a solid; 2. Reaction in a two layer system with the salt in the aqueous layer; 3. Reaction in hydroxylic solvents; 4. Reaction in highly polar aprotic solvents.

The objections which can be raised to a procedure according to point 1 are obvious. Procedures 2 and 3 suffer from the disadvantage that protic solvents readily solvate anions and thus decrease their reactivity. The reaction time will therefore be highly increased. If the anion is a strong base, protolytic side-reactions will also interfere.

At present, procedure 4 is the most popular one, especially with DMSO, DMF or HMPA as the solvent.¹ These solvents readily dissolve many salts and the anions have a very high reactivity since they are poorly solvated. This method has, however, several disadvantages: 1. The solvents are expensive and usually not readily recovered; 2. The reactions are often sensitive to traces of water; 3. In reactions with mesomeric anions these solvents tend to increase the extent of *O*-alkylation at the expense of *C*-alkylation. All these problems can be avoided if a salt is used which is soluble in water-immiscible organic solvents.

In recent years ion pair extraction has been used as an analytical method to extract anions from an aqueous layer into

chloroform or methylene chloride.² This possibility does not seem to have been realized by organic chemists although analytical data clearly indicate that most anions can be extracted as ion pairs with tetrabutylammonium as the cationic part. It has also been demonstrated by Brändström and Gustavii³ that the dimerisation of the ion pair in the organic solvent, which often occurs in concentrated solutions, highly improves the extractability of an ion pair.

On a preparative scale, ion pair extraction is a surprisingly simple procedure. One illustrative example, namely the synthesis of the tetrabutylammonium salt of methyl acetoxyacetate, is given below. In this example, the salt is isolated in crystalline form. For most purposes this is not recommended since the main losses occur in the recrystallisation step. The following anions have been extracted with tetrabutylammonium ion: cyanide, cyanate, azide, nitrite, iodide, bromide, benzoates, phenolates, and the enolates of β -diketones, β -cyanoesters, β -ketosulphones, and dimethyl benzoylmalonate. Preparative applications of these salts will be described in forthcoming publications.

Experimental. 238 g (0.7 mole) of tetrabutylammonium hydrogen sulphate (commercially available from Astra Meditec, Mölnådal, Sweden) was dissolved in 400 ml of water. A cold solution of 52 g (1.3 mole) of sodium hydroxide in 350 ml of water was added. A third solution of 86.5 g (0.6 mole) of methyl acetoxyacetate in 500 ml of chloroform was prepared. The solutions were mixed in a separatory funnel and shaken for 5 min. The layers were separated. The organic layer was treated with active carbon, dried with anhydrous magnesium sulphate, filtered and evaporated *in vacuo*. The residue, representing a quantitative yield, was recrystallized from acetone. Yellow crystals, 161 g, m.p. 140° (Kofler Heizbank), were obtained, representing a yield of 70 % of the tetrabutylammonium salt of methyl acetoxyacetate. The identity of the material was verified by NMR.

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